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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Emulsifier-Free Emulsion Polymers

(72) Gopferich, Achim - U.S.A. ;
Lee, Geoffrey - Germany (Federal Republic of) ;
Ludwig, Horst - Germany (Federal Republic of) ;
Schaffler, Achim - Germany (Federal Republic of) ;
Zierenberg, Bernd - Germany (Federal Republic of) ;

(73) Boehringer Ingelheim International G.m.b.H. - Germany (Federal Republic of) ;

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(57) 24 Claims

Abstract

The invention relates to emulsifier-free emulsion polymers, processes for their preparation and their use in pharmaceutical preparations giving a delayed release of active substance.

S012599.23

Emulsifier-free emulsion polymers

The present invention relates to emulsion polymers which are free from emulsifiers, processes for their preparation and their use in pharmaceutical preparations giving a delayed release of active substance.

Certain emulsion polymers, such as, for example, emulsion-polymerised esters of acrylic or methacrylic acid, have in recent years become indispensable adjuvants in the preparation of pharmaceuticals in which the intention is to provide a preparation with delayed release of the active substance [H. Determann und R. Lotz, Pharmazeutische Industrie 32 (1970) 469].

Delayed-release forms of this kind allow the active substance to be released constantly over a fairly long period and thus make it possible to reduce the number of doses of the drug to be administered each day and thereby simplify the therapy plan.

In the course of the development of these delayed release forms, in addition to numerous tablets and capsules, plasters which contain active substance with controlled release of the substance have also been described, inter alia.

Numerous methods are also known from the prior art for preparing delayed release forms of this kind.

For example, they may be prepared by freeing the emulsion polymer from the suspension agent, dissolving the polymer isolated in this way with the active substance in a suitable organic solvent, then evaporating off the solvent and grinding the solid polyacrylate, which contains the active substance, at a temperature below the glass transition temperature of the polymer, and processing the active substance-containing polyacrylate powder either by using tablet-making excipients to form tablets or in some other way, e.g. by introducing the powder into capsules.

The preparation of plasters which contain active substance is also known from the prior art, for example by processes described in European Patent No. 20 905.

Suitable emulsion polymers for producing such preparations include, as already mentioned hereinbefore, esters of acrylic or methacrylic acid, e.g. the commercially available products under the general product name of Eudragit made by Röhm GmbH of Darmstadt, Germany.

Emulsion polymers of this kind are generally produced by emulsifying the water-insoluble monomer in water with the aid of emulsifiers or surfactants and initiating or performing polymerisation with the use of conventional initiators. The polymer dispersions obtained by this kind of polymerisation can, in numerous instances, be used directly and are available in the form of dispersions. Active substance release systems produced on the basis of emulsion polymers of this kind do, however, have the disadvantage that the rate of release of the active substance may depend on the thermal treatment of the active substance release system during the manufacturing process and may also depend on the storage conditions.

The aim of the present invention is therefore to provide active substance release systems based on emulsion polymers - more particularly based on polyacrylic acid esters or polymethacrylic acid esters - which do not have the dependency described above and which also have substantially identical release characteristics even after lengthy storage under various storage conditions.

It has now been found, surprisingly, that the dependency of the rate of release on the thermal pretreatment during the manufacturing process, observed in the release characteristics of active substance release systems, can be traced back to the presence of the emulsifier.

A further aim of the present invention is to provide emulsifier-free emulsion polymers and a process for producing them.

According to the present invention, there is provided an emulsion polymer, which is substantially free from emulsifiers or surfactants and other adjuvants used in the preparation of said polymer.

According to a further aspect of the present invention there is provided a process for the preparation of an emulsion polymer as defined above wherein a dispersion of an emulsion polymer is first produced by conventional methods and in which the emulsifier, surfactant and other adjuvants used in the conventional preparation method (the extractable excipients) are subsequently substantially removed from said polymer dispersion.

There are various possible ways of removing the emulsifier and/or the other extractable excipients. In a preferred process according to the present invention, the emulsion polymer dispersion is treated with an extraction agent in which the polymer itself is insoluble and the extractable excipients are soluble. Preferably, water is used for the extraction methods according to the invention. However, depending on the type of polymer used, it is also possible to use other solvents or mixtures of solvents in which the polymer itself is insoluble.

For carrying out the extraction one may eliminate the emulsifier from the standard commercial emulsion by precipitating the polymer. This can be done by conventional methods, e.g. by precipitation with a suitable solvent or an acid, or by salting out, freezing out or extraction.

Another possibility is to remove the emulsifer or the other excipient(s) from the polymer after separation of the dispersing agent. The following methods would appear appropriate, for example:

equilibrium extraction, Soxleth extraction, column extraction or dialysis.

Alternatively, other methods of separation of the polymer such as centrifugation are suitable.

It is preferred to carry out extraction of the polymer, in particular the dried acrylate (Eudragit NE 30 D®).

In a preferred process according to the present invention, the dried acrylate is comminuted or ground in a suitable apparatus and extracted with water, which is constantly renewed. Preferably, the emulsifier is eliminated by freezing the corresponding emulsion polymer and subsequently thawing it and washing with a suitable solvent, preferably water.

The emulsion polymers of the present invention may be used in the production of active substance release systems which use comprises a further feature of the present invention. The emulsifier-free active substance release systems are produced therefrom, by methods known per se.

According to a further aspect of the present invention there is provided an active substance release system based on an emulsion polymer which contains an emulsion polymer as defined above. A preferred release system according to the present invention is one which provides delayed release of the active substance.

According to a yet further aspect of the present invention there is provided a process for the preparation of an active substance release system as defined above, wherein one or more emulsion polymers as defined above is or are charged with one or more active substances in a manner known per se.

As already mentioned, the preparation of the active substance release systems is known from the prior art and described, inter alia, in German Offenlegungsschrift 33 14 003 and in European Patent 0 086 997, the contents of which are referred to here.

Suitable carriers, in addition to the polymers mentioned hereinbefore, are those polymers which can be prepared by the emulsion polymerisation method, e.g. PVC, polylactides, polystyrene, polyvinylacetate, polybutadiene, polyacrylonitrile, polyvinylpyrrolidone, polyvinylester, polyvinylether and copolymers thereof. Polymers based on esters of acrylic and/or methacrylic acid are preferred.

Emulsion-polymerised copolymers of methyl and/or ethylesters of acrylic and methacrylic acid are particularly preferred.

Examples of pharmaceutical active substances include, as well as clonidine, ranitidine, cimetidine, atenolol, enalapril, captopril, nifedipine, naproxene, diclofenac, diclofenac sodium, piroxicam, cefaclor, diltiazem, ketotifene, ketotifene-hydrogen fumarate, salbutamol, propranolol, amoxicillin, triamterene, norethisterone, mestranol, cefotoxamine, cefotoxamine-sodium, ceftriaxone, ceftriaxone-disodium, cefalexin, dipyridamole, alprazolam, cefoxitin, cyclosporin, metoprolol tartrate, acyclovir, sulindac, clavulanic acid, methyldopa, nicardipine, pentoxifylline, glycerol trinitrate, timolol, idebenone, terfenadine, tamoxifen-dihydrogen citrate, prazosine, doxorubicine, amiloride, amiloride.HCl, hydrochlorothiazide, dihydroergocornine, dihydroergocornine methanesulphonate, erythromycin, erythromycin stearate, triazolam, latamoxef, cromoglycic acid, ceftazidime, clenbuterol, bromhexine oxytetracycline, dexamethason-21-isonicotinate, sulfadiazine, cimaterol, aditoprim, mederantil, climazolam, carprofen, caffeine and acetylsalicyclic acid - or vitamins - such as vitamin A, A_1, A_2, B_1, B_2, B_4, B_6, B_{12}, C (ascorbic acid), ascorbylpalmitate and other pharmacologically acceptable derivatives of ascorbic acid, D, D_1, D_2, D_3, D_4, E, H, K, K_1, K_2, P and Q - or active substances such as avoparcine, flavopholipol, monensine, monensine-sodium, salinomycin,

carbadox, nitrovin and olaquindox, and active substances such as those mentioned in the Red List 1990 (Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH und Co. KG, Aulendorf/Württemb.) the contents of which are hereby referred to.

For the preparation of the active substance release system according to the present invention, the emulsion polymer as defined above is usually dissolved with the active substance in a suitable organic solvent, the solvent is evaporated off and the solid, active substance-containing polyacrylate is further processed depending on the planned use.

The measured values of the particular rates of release found were recorded after the following treatment of the samples: the first measured value was recorded after treatment of the samples with artificial gastric juice at pH : 1.2 over a period of one or two hours - all the subsequently measured values were recorded after treatment of the samples with artificial intestinal juice at pH : 6.5 after the periods of time respectively indicated.

The present invention is further illustrated by reference to Figures 1 to 13. These Figures will now be discussed and their relevance explained:

Figs. 1 to 10 show the influence of the thermal pretreatment and storage time on the rates of release of active substance from emulsifier-containing or emulsifier-free active substance release systems produced on the basis of polyacrylate (Eudragit). In each case the active substance is clonidine.

Figs. 1 to 5, 8 and 10 show the release characteristics of various active substance preparations consisting of 1.00 wt.-% of clonidine and 99.00 wt.-% of acrylate. Figs. 6, 7 and 9 show the release characteristics of corresponding polyvinylpyrrolidone-

containing active substance release systems.

In each particular case, the acrylate used was an untreated polyacrylate, or a polyacrylate freed from dispersant, the acrylate being of the make Eudragit NE 30 D® of Röhm GmbH of Darmstadt, Germany. The particle size of the preparation in question is in the range from 315-400 µm. The quantity of active substance contained therein amounts to 130 µg.

Fig. 11 and Fig. 12 show the dependency of the diffusion coefficient on the charge, on the one hand using a non-extracted matrix (Fig. 11) and on the other hand using an extracted matrix (Fig. 12).

Fig. 13 shows the rates of release of an active substance release system charged with clenbuterol (8 wt.-%). (Matrix: Eudragit NE 30 D).

In the Figures 1 to 9, the various symbols used denote the following:-

Ch 20/U represents an untempered sample measured after drying at 20°C.

Ch 40/U represents an untempered sample measured after drying at 40°C.

Ch 20/T represents a sample which is tempered for a period of 1 hour (Figs. 8a and 9a) or 3 hours (remaining Figures) at 70°C after drying at 20°C and then measured.

Ch 40/T represents a sample which is tempered for a period of 1 hour (Figs. 8a and 9a) or 3 hours at 70°C after drying at 40°C and then measured.

Ch 20/O represents a sample dried at 20°C and tempered for a period of 15 hours at 70°C and subsequently

measured.

Ch 20/0.5/20 represents a sample dried at 20°C and tempered at 70°C for a period of 15 hours and measured after a storage time of half a month, at 20°C.

Ch 20/1/20 represents a sample dried at 20°C and tempered at 70°C for a period of 15 hours and measured after a storage time of one month at 20°C.

Ch 20/2/20 represents a sample dried at 20°C and tempered at 70°C over a period of 15 hours and measured after a storage time of two months at 20°C.

Ch 20/4.5/20 represents a sample dried at 20°C and tempered at 70°C over a period of 15 hours and measured after a storage time of four and a half months at 20°C.

Ch 20/6/20 represents a sample dried at 20°C and tempered at 70°C over a period of 15 hours and measured after a storage time of six months at 20°C.

Ch 20/7/40 represents a sample dried at 20°C and tempered at 70°C for a period of 15 hours and measured after a storage time of 7 days at 40°C.

Ch 20/14/40 represents a sample dried at 20°C and tempered at 70°C for a period of 15 hours and measured after a storage time of 14 days at 40°C.

Ch 20/30/40 represents a sample dried at 20°C and tempered at 70°C over a period of 15 hours and measured after a storage time of 30 days at 40°C.

Ch 20/60/40 represents a sample dried at 20°C and tempered at 70°C over a period of 15 hours and measured after a storage time of 60 days at 40°C.

Ch 20/180/40 represents a sample dried at 20°C and tempered at 70°C over a period of 15 hours and measured after a storage time of 180 days at 40°C.

Ch 40/0 represents a sample dried at 40°C and tempered for a period of 15 hours at 70°C and subsequently measured.

Ch 40/0.5/20 represents a sample dried at 40°C and tempered at 70°C for a period of 15 hours and measured after a storage time of half a month at 20°C.

Ch 40/1/20 represents a sample dried at 40°C and tempered at 70°C for a period of 15 hours and measured after a storage time of one month at 20°C.

Ch 40/2/20 represents a sample dried at 40°C and tempered at 70°C for a period of 15 hours and measured after a storage time of two months at 20°C.

Ch 40/6/20 represents a sample dried at 40°C and tempered at 70°C for a period of 15 hours and measured after a storage time of six months at 20°C.

Ch 40/0.5/40 represents a sample dried at 40°C and tempered at 70°C for a period of 15 hours and measured after a storage time of half a month at 40°C.

Ch 40/1/40 represents a sample dried at 40°C and tempered at 70°C for a period of 15 hours and measured after a storage time of one month at 40°C.

Ch 40/2/40 represents a sample dried at 40°C and tempered at 70°C for a period of 15 hours and measured after a storage time of two months at 40°C.

Ch 40/6/40 represents a sample dried at 40°C and

tempered at 70°C for a period of 15 hours (Fig. 5) or 3 hours (Fig. 7b) and measured after a storage time of six months at 40°C.

Ch 20/6/40 represents a sample which was dried at 20°C, tempered for 3 hours at 70°C, stored for six months at 40°C and measured.

Ch 40/T/3/40 represents a sample which had been heated to a temperature of 70°C for 3 hours and was measured after 3 months storage at 40°C.

Ch 40/U/3/40 represents an untempered sample which was measured after 3 months storage at 40°C.

In Figure 10 the symbols used denote the following:-

Ch W represents an untempered sample, prepared directly from the aqueous dispersion, which had been dried at a temperature of 20°C and measured immediately.

Ch W/3/20 represents an untempered sample prepared directly from the aqueous dispersion, which had been stored for a period of three months at a temperature of 20°C after manufacture and then measured.

Ch W/3/40 represents an untempered sample prepared directly from the aqueous dispersion, which had been stored for a period of three months at a temperature of 40°C after manufacture and then measured.

As previously indicated, for Figures 6, 7 and 9, the samples contain polyvinylpyrrolidone.

Fig. 1 shows the rates of release of preparations containing emulsifier which have not been tempered or

have been tempered for 3 hours at 70°C (melting of the emulsifier) and have been dried at temperatures of 20°C or 40°C, respectively, as a function of time. Fig. 1 clearly shows that the rates of release of untempered matrices containing emulsifier assume their maximum values, with a given time span, whilst the rates of release of the preparation dried at 20°C are comparatively higher than those of the active substance preparation dried at 40°C. By contrast, the rates of release of the tempered samples show significantly lower levels.

Fig. 2 shows the rates of release of emulsifier-containing active substance preparations which have been dried at 20°C and tempered for 15 hours at 70°C and stored for various lengths of time at a temperature of 20°C.

It can be seen from Fig. 2 that the rates of release of the merely tempered sample show the lowest values, whilst the rates of release of samples stored for a longer period at 20°C are significantly higher than the values for the completely untreated matrix or the merely tempered matrix.

Fig. 3 shows the rates of release of active substance preparations containing emulsifier which have been dried at 20°C and tempered for 15 hours at 70°C and, unlike Fig. 2, stored for various lengths of time at a temperature of 40°C.

In principle, Fig. 3 shows that the various active substance preparations behave analogously.

Fig. 4 shows the rates of release of an active substance preparation which had been treated analogously to the preparation in Fig. 2 but unlike the former had been

dried at 40°C. Fig. 4 also shows that the rates of release increase as the storage time of the samples increases, so that the sample which had been stored for 6 months at 20°C showed the highest rates of release. By contrast, the sample which was measured immediately (0 months) showed the smallest release levels.

Fig. 5 shows the rate of release of an active substance preparation which had been treated analogously to the preparation in Fig. 3 but, unlike the former, had been dried at 40°C. In principle, the same tendencies can be found in Fig. 5 as in Fig. 4.

Fig. 6 shows the release characteristics of a polyvinylpyrrolidone-containing matrix which contains emulsifier, having the composition: 1 wt.-% clonidine, 20 wt.-% polyvinylpyrrolidone and 79% acrylate (Eudragit NE 30 D®) which had been dried at 20 or 40°C, in tempered or untempered form.

The measurements of the release rates were recorded after the following treatment of the samples:

1) 1 hour in artificial gastric juice - pH: 1.2;

2) 1 hour in artificial intestinal juice - pH: 6.5;

3) a further 2 hours in artificial intestinal juice - pH: 6.5;

4) a further 2 hours in artificial intestinal juice - pH: 6.5.

Fig. 6 also shows that, irrespective of the presence of polyvinylpyrrolidone, the rates of release of the tempered samples are significantly lower than those of the untempered active substance release

systems.

Figures 7a and 7b also show the influence of various drying conditions. The composition of all the samples consists of 1.00% clonidine, 20.00 wt.-% polyvinylpyrrolidone and 79% acrylate. The samples were all treated analogously to the method given in the description of Fig. 6 in order to record the release characteristics.

Fig. 7a shows the release characteristics of an untreated sample, a sample which had been melted at 70°C for 3 hours, and a sample which had been melted for 3 hours at 70°C and stored for 6 months at a temperature of 40°C. All the samples were dried at a temperature of 20°C.

Fig. 7b shows the release characteristics of samples which had been treated analogously to those in Fig. 7a, except that they were dried at a temperature of 40°C.

Fig. 8a shows the rates of release of an active substance release system the matrix of which had been freed from emulsifier.

The release system is made up of 1.00 wt.-% clonidine and 99.00 wt.-% emulsifier-free acrylate. The measurements of the release rates were each recorded after the following treatment of the samples:

1) 2 hours in artificial gastric juice - pH: 1.2;

2) a further 2 hours in artificial intestinal juice - pH: 6.5;

3) a further 2 hours in artificial intestinal juice - pH: 6.5;

4) a further 2 hours in artificial intestinal juice - pH: 6.5;

5) a further 16 hours in artificial intestinal juice - pH: 6.5.

The rates of release of samples are given which had been dried at different temperatures (20°C and 40°C) and which had been used untempered or after tempering for one hour at 70°C.

Figure 8b shows the release characteristics of an active substance release system (composition as described under Fig. 8a) based on an emulsifier-free matrix after 3 months storage at a temperature of 40°C.

Fig. 9a shows the release characteristics of polyvinyl-pyrrolidone-containing active substance release systems free from emulsifier, made up of 1.00 wt.-% clonidine, 20.00 wt.-% polyvinylpyrrolidone and 79.00 wt.-% acrylate.

The measurements of the release rates in question were recorded after the following treatment of the samples:

1) 1 hour in artificial gastric juice - pH: 1.2;

2) a further hour in artificial intestinal juice - pH: 6.5;

3) a further 2 hours in artificial intestinal juice - pH: 6.5;

4) a further 2 hours in artificial intestinal juice - pH: 6.5;

5) a further 18 hours in artificial intestinal juice - pH: 6.5.

The rates of release of samples were recorded which had been dried at different temperatures and which were used untempered or after tempering for one hour at 70°C.

Fig. 9b shows the release characteristics of an active substance release system (composition as described under 9a) based on an emulsifier-free matrix after three months storage at a temperature of 40°C.

Figs. 8 and 9 show that the thermal treatment and storage time have a negligibly slight influence on active substance release systems which are free from emulsifier.

Fig. 10 shows the release characteristics of an active substance release system prepared directly from the aqueous dispersion (composition: 1 wt.-% clonidine, 99 wt.-% acrylate), which had been measured immediately after manufacture and after three months' storage at 20°C or 40°C, respectively.

As can be seen from the Figures described above, for the emulsifier-containing active substance release systems, the release rates are dependent on the thermal treatment of the active substance release system. Thus, the release rates of the untempered samples are significantly higher than those which have been tempered for three hours at 70°C. At the same time, it is apparent that the release rates of the samples (both tempered and untempered) which have been dried at 20°C are higher than the corresponding rates for those samples which have been dried at 40°C.

The release functions graphically shown in Figs. 2 to 5 indicate that the following trend can be found,

irrespective of the drying temperature (20°C or 40°C) and storage temperature (20°C or 40°C) in tempered samples (70°C): the release rates of those samples which were measured immediately after tempering are by far the lowest release rates. They are significantly below the levels obtained for the corresponding untempered samples. As the storage time increases, the rates of release generally increase at different levels (depending on the drying and storage temperature.

Figs. 6 and 7 show the influence of the emulsifier on the release rates in a polyacrylate/polyvinyl-pyrrolidone mixture, of a kind which is commercially sold. The findings drawn from Figs. 1 to 5 are also confirmed by the release rates of these systems. Thus, the release rates of the tempered samples are below those of the untempered samples and again there is a dependency on the drying temperature. In these cases, too, the release rates increase after several months' storage.

A completely different picture emerges, on the other hand, when the same investigations are made of emulsifier-free systems for releasing active substance (Figs. 8a and 9a). Independently of the drying conditions, the release rates, both in the PVP-containing system and in the PVP-free system, show only slightly different values, and in both cases the difference from values of the tempered samples proves to be negligibly slight.

It is also illustrated (Figs. 8b and 9b) that the active substance release systems prepared according to the invention show better durability, i.e. the release rates remain substantially unaffected even by lengthy storage of the active substance release system.

Fig. 11 shows the dependency of the diffusion coefficient on the load for a non-extracted matrix (Eudragit NE 30 D).

Fig. 12 shows this dependency for the corresponding extracted matrix-material. It is clearly visible that, for the purified polymer (Fig. 12) there is substantially smaller scattering with regard to the diffusion coefficient than for the corresponding, non-extracted acrylate.

Fig. 13 also provides clear evidence that the release from extracted matrices is significantly slower - with less scattering between the curves - than from the corresponding non-extracted matrix.

Thus, in conclusion, by extracting the emulsifier, it can be seen that it is possible to obtain release characteristics which are independent of the thermal treatment of the release system. The aims of the present invention mentioned hereinbefore may therefore be achieved.

The process of the present invention is further illustrated in the following Example 1. Various other embodiments of the process will be apparent to the person skilled in the art from the foregoing description. However, it is expressly indicated that the Example and the specific description thereof are provided solely for the purpose of explanation and description and should not be regarded as restricting the scope of the invention.

Example 1

30.0 g of the aqueous Eudragit NE 30 dispersion are frozen at -18°C and then thawed by simply standing at ambient temperature. After it has thawed completely, demineralised water is added to 300.0 g, with stirring. As a result of this treatment, the dispersion is broken up completely and a clear supernatant is formed over a loose white deposit. (Any slight turbidity present can be clarified by separating suspended particles using a suction device.) The supernatant is decanted and replaced by the same amount of demineralised water and the residue is washed therewith for about 1 minute. Separation, topping up and washing are repeated as often (9 times) as is necessary for the last two aqueous wash media separated off to be free from emulsifier. (Instead of adding 10 times the amount of washing water, it is also possible to wash 15 times with three times the amount of water. The last washing water will then be demonstrably free from emulsifier.).

Claims

1. An emulsion polymer, which is substantially free from emulsifiers or surfactants and other adjuvants used in the preparation of said polymer.

2. An emulsion polymer as claimed in claim 1 wherein the polymer is based on esters of acrylic and/or methacrylic acid.

3. An emulsion polymer as claimed in claim 1 or claim 2 wherein the polymer is based on the methyl and/or ethylester of acrylic and/or methacrylic acid.

4. An emulsion polymer as claimed in claim 1 wherein the polymer is selected from the group comprising polylactide, polystyrene, polyvinylacetate, polyvinylpyrrolidone, polybutadiene, polyacrylonitrile, the polyvinylesters, the polyvinylethers and copolymers thereof and mixtures thereof.

5. An emulsion polymer as claimed in any of claims 1 to 4 specifically as described herein.

6. A process for the preparation of an emulsion polymer as claimed in any of claims 1 to 5 wherein a dispersion of an emulsion polymer is first produced by conventional methods and in which the emulsifier, surfactant and other adjuvants used in the conventional preparation method (the extractable excipients) are subsequently substantially removed from said polymer dispersion.

7. A process as claimed in claim 6 wherein the extractable excipients are separated from the emulsion polymer by treating the dispersion with an extraction agent in which the polymer itself is insoluble or

substantially insoluble and the extractable excipients are soluble or substantially soluble and either the polymer or the extractable excipients are subsequently removed from the dispersion.

8. A process as claimed in claim 7 wherein the extraction agent is water.

9. A process as claimed in claim 7 or claim 8 wherein the polymer is removed from the dispersion by precipitation.

10. A process as claimed in claim 9 wherein the polymer is precipitated by means of a suitable solvent or acid or by salting out or by freezing.

11. A process as claimed in claim 7 or claim 8 wherein the polymer is removed from the dispersion by centrifugation.

12. A process as claimed in claim 7 or claim 8 wherein the extractable excipients are removed from the dispersion by equilibrium extraction, Soxleth extraction, column extraction or dialysis.

13. A process as claimed in any of claims 6 to 12 substantially as herein described.

14. A process as claimed in any of claims 6 to 12 substantially as herein described and with reference to the Example.

15. An emulsion polymer as claimed in claim 1 whenever prepared by a process as claimed in any of claims 6 to 14.

16. An active substance release system based on an

emulsion polymer which contains an emulsion polymer as claimed in any one of claims 1 to 5 or 15.

17. A release system as claimed in claim 16 characterised in that it gives delayed release of the active substance.

18. An active substance release system as claimed in claim 16 or 17 wherein the active substance is clonidine (2-[(2,6-dichlorophenyl)-imino]imidazolidine).

19. An active substance release system as claimed in claim 16 or 17 wherein the active substance is clenbuterol (4-amino-α-[(tert.-butylamino)-methyl]-3,5-dichlorobenzyl alcohol).

20. The use of a polymer as claimed in any of claims 1 to 5 in an active substance release system as claimed in any one of claims 16 to 19.

21. A process for the preparation of an active substance release system as claimed in any one of claims 16 to 19, wherein one or more emulsion polymers as claimed in any one of claims 1 to 5 or 15 is or are charged with one or more active substances in a manner known per se.

22. A process as claimed in claim 21 substantially as herein described.

23. Each and every novel product, process, method and use herein described.

24. A process for the preparation of an emulsion polymer as claimed in any one of claims 1 to 4, which process comprises subjecting a polymerizable monomer to emulsion polymerization and separating from the obtained polymer all or substantially all of the emulsifier or surfactant used in the polymerization.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

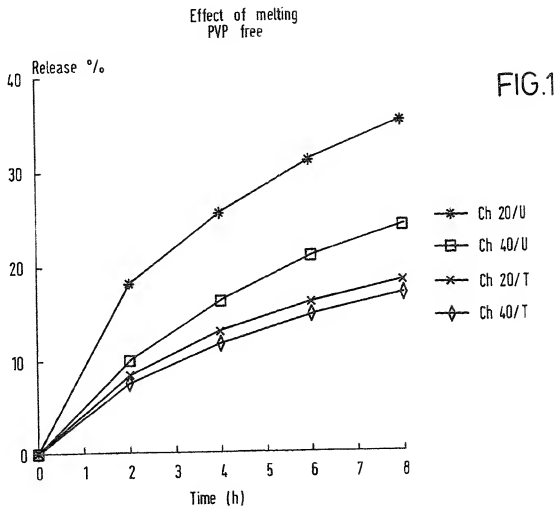

FIG.1

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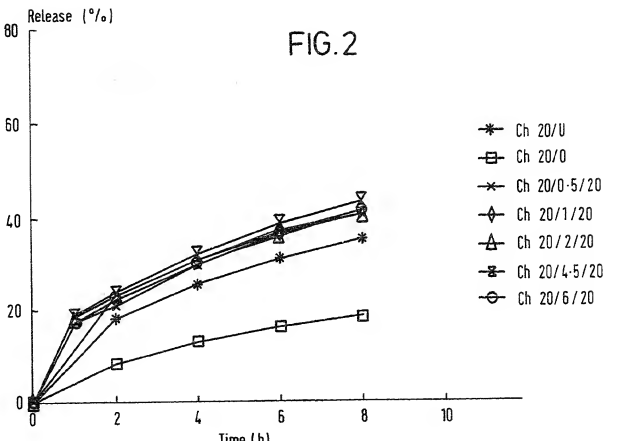

FIG. 2

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FIG.3

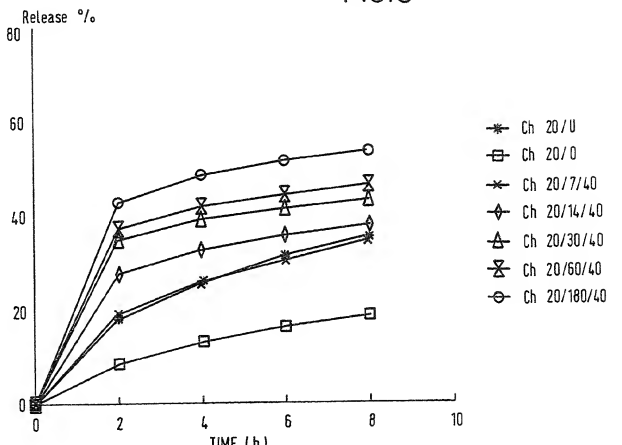

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FIG. 4

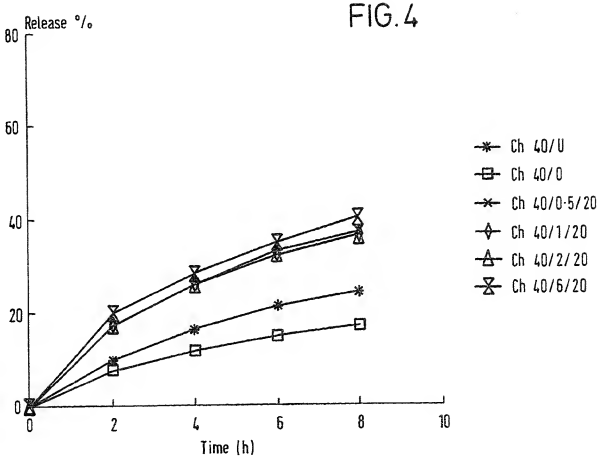
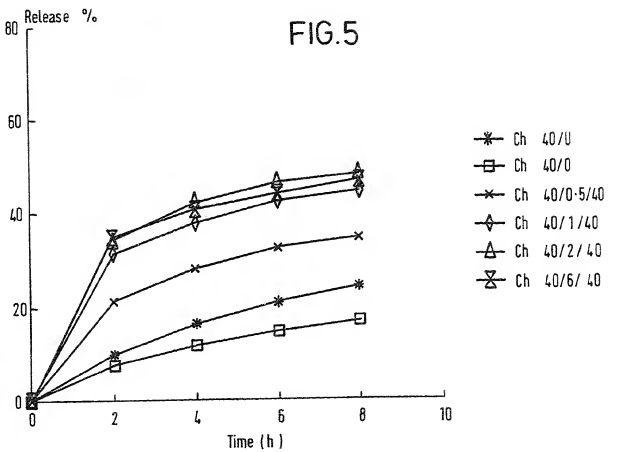


FIG.5



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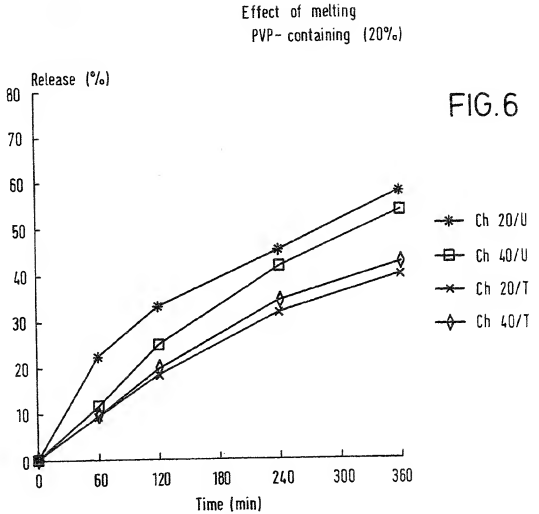


FIG.6

FIG.7a

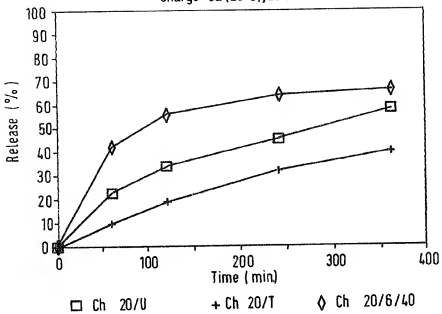
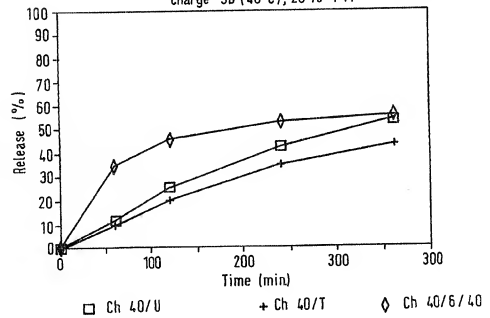


FIG.7b



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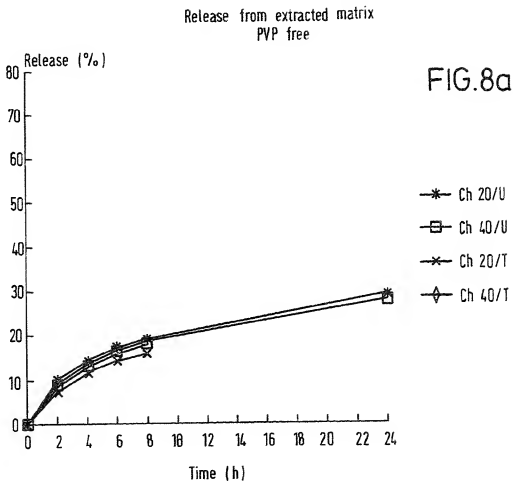
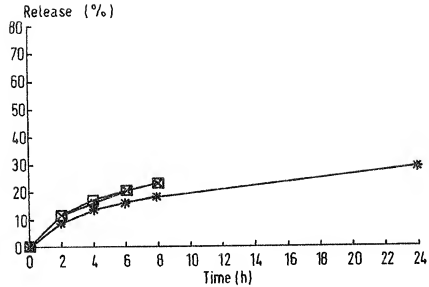


FIG.8a

FIG.8b



Release of clonidine from extracted (emulsifier-free) matrix, effect of tempering at 40°C

- ✱ Untempered : Ch 40/U
- □ 3h 70°C,3MoN.40°C : Ch 40/T/3 /40
- × 3 Mon. 40°C : Ch 40/U/3/40

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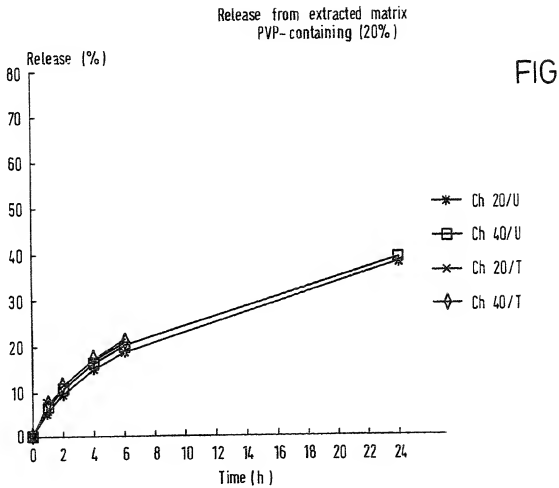


FIG.9a

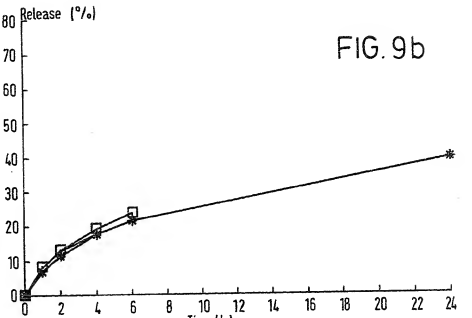


FIG. 9b

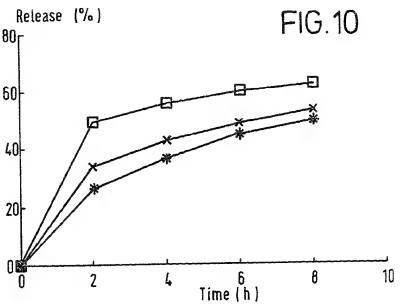
Release of clonidine from extracted (emulsifier - free) matrix, effect of tempering at 40°C

* Untempered : Ch 40/U

□ 3h 70°C, 3Mon. 40°C : Ch 40/T/3/40

× 3 Mon. 40°C : Ch 40/U/3/40

FIG.10



Release from matrices on an aqueous basis, effect of storage

*	Ch W
□	3Mon. 20°C Ch W 3/20
×	3Mon. 40°C Ch W 3/40

FIG. 11

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FIG.12

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FIG.13